Facile Synthesis of 5-Carboxylate Substituted Piperazin-2-ones as Peptidomimetic Agents

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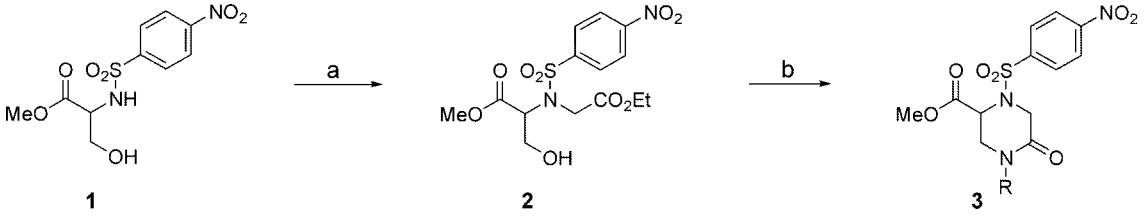
Recent progress in conformationally-restricted peptidomimetics with biologically active molecules points toward the need for progress with new and diverse small-molecular scaffolds possessing appreciated substituents at various positions.[1] The introduction of piperazinones has been actively pursued in recent years due to the importance of this class of compound in this field. Piperazinones are widely applicable to the development of peptidomimetic drugs in medicinal chemistry, including enzyme inhibitors, peptide secondary structure mimetics and combinatorial libraries. A literature survey on the preparation of piperazinones shows that a variety of methods have been reported based on cyclization of functionalized ethylenediamines with α-haloacetic acid derivatives[2a-d] or organoboronic acids,[2e] intramolecular cyclization of peptidic analogous[3a-q] and condensation of *N*-(chloroethyl)glycinate with amines.[4] Nevertheless, there are relatively few synthetic methods for the preparation of piperazinones by tandem cyclization with amines.[2a,4,5]

In the present paper, we report the reaction of sulfonamide-protected serine derivative **2** with mesyl chloride, followed by the addition of a primary amine, which leads to the formation of piperazin-2-ones **3** in one pot. This reaction proceeded through tandem β-elimination of the mesylate-activated hydroxyl group, conjugate addition of the enone with amines and cyclization under mild condition.

A synthetic route for new piperazin-2-ones **3** is outlined in Scheme 1. The synthesis was carried out using 4-nitrobenzenesulfonyl-protected serine methyl ester **1** as the starting material. Compound **1** was readily prepared from serine methyl ester and 4-nitrobenzenesulfonyl chloride, a versatile protecting group of amines.[6] Compound **1** was alkylated efficiently under the conventional condition (K_2CO_3, DMF, rt) to give methyl 2-[ethoxycarbonylmethyl-(4-nitro-benzenesulfonyl)-amino]-3-hydroxy-propionate **2** in good yield (86 %). The hydroxyl group of compound **2** was activated with mesyl chloride, followed by the addition of primary amines smoothly converted to the piperazin-2-ones **3** in one pot.

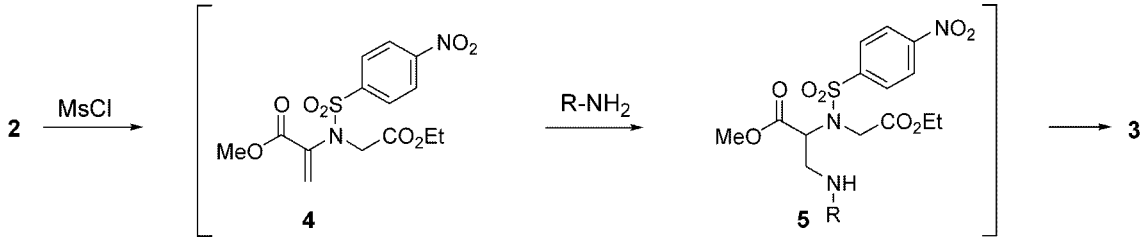
We expected that the reactions might undergo a tandem direct S_N2 displacement of activated hydroxyl group with primary amines and cyclization of the ethyl ester with the resulting secondary amines. However, with careful scrutiny of the reaction, we found that the reaction took place exclusively through conjugate addition of the enone **4** rather than the intermediate of S_N2 displacement (Scheme 2).

The dehydration of β-hydroxyamino acid derivatives is well known,[7] and we could detect the enone compound **4** in



1 **2** **3**

Scheme 1. (a) Ethyl bromoacetate, K_2CO_3, DMF; (b) MsCl, Et_3N, CH_2Cl_2; R-NH_2, CH_2Cl_2.



4 **5**

Scheme 2

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Table 1. Tandem cyclization reaction of the compound **2** toward piperazin-2-ones **3**

Entry	Amine[a]	Product	Yield (%)[b]
1	Ammonium hydroxide	**3a** (R=H)	64
2	Methylamine	**3b** (R=CH_3)	72
3	Benzylamine	**3c** (R=CH_2Ph)	68
4	Allylamine	**3d** (R=$CH_2CH=CH_2$)	69
5	Cyclopropylamine	**3e** (R=$CH(CH_2)_2$)	74
6	Ethanolamine	**3f** (R=CH_2CH_2OH)	85
7	Glycine *t*-butyl ester HCl	**3g** (R=CH_2CO_2tBu)	89
8	Aniline	**3h** (R=Ph)	0

[a]Amine was diluted with CH_2Cl_2 or dioxane (for aqueous amine), and added to the reaction mixture. [b]These isolated yields are not optimized.

TLC during the reaction. Compound **4** was isolated and characterized by NMR experiments.[8]

To explore the scope of the reaction, a series of piperazin-2-ones differing only at the R amide position was prepared (Table 1). Most aliphatic primary amines afforded piperazin-2-ones **3** in good yield under the standard reaction conditions,[9] even with aqueous amines. An amine containing reactive functionality, such as alcohol (entry 6), was well tolerate in the reaction condition. In the case of aniline (entry 8), the reaction resulted in the accumulation of only β-eliminated compound **4**. Because of poor nucleophilicity of aniline, the conjugate addition might not proceed in the reaction conditions. In our reaction, under the conjugate addition condition, the cyclization of the intermediate **5** took place in tandem mode.

To the best of our knowledge, this could be the first example of a tandem β-elimination-conjugate addition-cyclization reaction to prepare piperazin-2-ones from hydroxyl-ester compounds in one pot. The advantages of this method are really simple and give good overall yields for the preparation of piperazin-2-ones **3**. Furthermore, the reaction is an efficient and convenient method for the preparation of piperazin-2-one analogous with structural diversity of R-groups at the amide position due to the wide availability of amine components.

In conclusion, a facile synthesis of 5-carboxylate substituted piperazin-2-ones has been developed. Our strategy allows the introduction of a variety of substituents at the amide N-position. Applications for the preparation of conformationally-restricted peptides and enzyme inhibitors, which exhibited anti-angiogenic activity, have been achieved and will be reported in due course.

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8. **4**: yellowish crystal, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.0 Hz, 3H), 3.70 (s, 3H), 4.18 (q, 2H), 4.31 (s, 2H), 6.19 (s, 1H), 6.55 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 8.8 Hz, 2H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 50.4, 52.6, 61.6, 123.9, 128.9, 132.1, 134.7, 144.9, 150.1, 163.2, 168.3; MS (m/e) 373 (M^++1), 313, 299, 249, 186, 122, 76, 54; m.p. 100-101 ^{o}C.
9. Representative procedure: **3a**: To a solution of **2** (0.40 g, 1.0 mmmol) and Et_3N (0.47 mL, 3.4 mmol) in 15 mL of CH_2Cl_2 at 0 ^{o}C was added dropwise methanesulfonyl chloride (0.10 mL, 1.3 mmol). After stirring for 3 h at rt, ammonium hydroxide (28%, 0.39 mL, 3.0 mmol) solution diluted with 10 mL of dioxane was added dropwise at 0 ^{o}C. After stirring for 16 h at rt, H_2O (20 mL) was added, and the mixture was partitioned. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallization from ethyl acetate/hexane provided piperazinone **3a** as a white solid (0.22 g, 64% yield). ^{1}H NMR ($CDCl_3$+CD_3OD, 400 MHz) δ 3.61 (s, 3H), 3.76 (br s, 2H), 3.89 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 17.1 Hz, 1H), 4.91 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 8.40 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz) δ 43.6, 45.7, 53.2, 53.6, 124.5, 128.9, 143.6, 150.5, 165.8, 168.7; MS (m/e) 344 (M^++1), 284, 186, 157, 122, 97, 76, 69; m.p. 184 ^{o}C.